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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,145	04/16/2001	Benjamin F. Cravatt	SCRIP1210-3	7817

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EXAMINER	
EPPERSON, JON D	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/10/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
File Copy	09/836,145	CRAVATT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-11,13,15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,16-18 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on July 2, 2003 (Paper No. 18).

Status of the Claims

2. Claims 1-24 are pending in the present application.

3. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 10 is acknowledged (Applicant elected Group IV, claims 12-13 and new claims 14-24) and claims 1-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

4. Please note: Applicant's elected species (e.g., see Paper No. 18) was searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine

patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claims 13, 15 and 19 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (see below i.e., ***Response to Restriction and/or Election of Species***).

6. Therefore, claims 12, 14, 16-18 and 20-24 are examined on the merits in this action.

Response to Restriction and/or Election of Species

7. Applicant's election of Group I (claims 12-24) with traverse in Paper No. 10 is acknowledged.

8. The traversal is on the ground(s) that "Groups I-IV are intimately related" because they have overlapping subject matter and, as a result, "no conservation of patent office resources would be realized if the present restriction is maintained" (see Paper No. 10, page 2, paragraph 1).

9. These arguments were fully considered but were not found persuasive. While there is overlapping subject material. The searches would not be coextensive because there is also non-overlapping subject material and, as a result, this would create an undue burden for the Office. As stated previously, the different Groups encompass divergent subject matter (see Paper No. 7,

paragraphs 1-6) that would require different searches and there is no expectation that the searches would be coextensive. The Examiner maintains that this does create an undue search burden.

10. Applicant's election of species in Paper Nos. 10, 15 and 18 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

11. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Priority Claims

12. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

This application is a CON of 09/738,271, which claims benefit of 60/195,954, 60/212,891 and 60/222,532. However, the provisional applications upon which benefit is claimed (i.e., 60/195,954, 60/212,891 and 60/222,532) fail to provide adequate support under 35 U.S.C. 112 for the claims of this application. In the instant case, provisional applications 60/195,954 and 60/212,891 fail to disclose "activity based probes" wherein F is a sulfonyl group. Furthermore, although provisional application 60/222,532 does disclose "activity based probes" wherein F is a "sulfonate" (e.g., see claim 29) it does not provide support for the broader

"sulfonyl group" claim. If applicant believes this to be in error, applicant must disclose where in the specification support for the broader "sulfonyl group" term can be found (i.e., indicate, page, paragraph and line numbers for each provisional application). Therefore the filing date of the instant application is deemed to be the filing date of the 09/738,271 CON i.e., **December 15, 2000**.

Information Disclosure Statement

13. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

14. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

15. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code such (e.g., see page 42, paragraph 41; see also page 68, paragraph 205, and others throughout the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

16. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 12, 14, 16-18 and 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claims 12, 14** recite the limitation "said complex mixture." There is insufficient antecedent basis for this limitation in the claims. The Examiner recommends, "said complex mixture of proteins". Therefore, claims 12, 14 and all dependent claims are rejected under 35 USC 112, second paragraph.

B. **Claims 12, 14** recite the limitations "said functional group" and "said sulfonyl group." There is insufficient antecedent basis for these limitations in the claims. The Examiner recommends, "said sulfonyl functional group". Therefore, claim 12 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. **Claim 12** recites the limitation "said library" and "said combinatorial library." There is insufficient antecedent basis for these limitations in the claims. The Examiner

recommends, "said combinatorial chemical library" (for claims 12). Therefore, claims 12 and all dependent claims are rejected under 35 USC 112, second paragraph.

D. **Claim 12** recites the limitation "said active and inactivated complex mixture", "said inactivated complex mixture" and "said active complex mixture." There is insufficient antecedent basis for these limitations in the claims. Therefore, claim 12 and all dependent claims are rejected under 35 USC 112, second paragraph.

E. For **claim 12**, the phrase "combining with said complex mixture, in an active form and an inactivated form, said combinatorial chemical library" is vague and indefinite. For example, it is not clear whether the "active form and inactivated form" refer to the "complex mixture" or the "chemical library"? Applicants are requested to clarify. Therefore, claim 12 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

F. **Claim 14** recites the limitation "the total target protein." There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 14 and all dependent claims are rejected under 35 USC 112, second paragraph.

G. **Claim 23** recites the limitation "said second portion of said complex proteomic mixture." There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 23 and all dependent claims are rejected under 35 USC 112, second paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 12, 14, 16-18 and 20-24 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

The present claims are directed to the use of "non-directed" R*(F-L)-X activity based probes for screening combinatorial chemical libraries wherein X is "a ligand", "L- a bond or alkylene or an alkyleneoxy chain linking group", F is "a sulfonyl group" and R is "a group of less than 1 kDal." These claims represent broad scope because they would include an infinite number of methods for producing and/or using an infinite number of structural variants (i.e., activity based probes) wherein no distinguishing structural attributes are provided for the "R" and "X" portions of the "activity based probes." The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "R" and "X" portions of the "activity based probes." Furthermore, Applicants' claims include method steps for the identification of an infinite number of "active target proteins" wherein no distinguishing structural features are provided for these proteins either.

In contrast, Applicants specification is narrow in scope disclosing only one "non-directed" library of "activity based probes" (i.e., containing eleven members of biotinylated

sulfonate esters) that was useful in identifying one target protein (i.e., class I aldehyde dehydrogenase, cALDH-I, was irreversibly inhibited by the sulfonate library). Here, all eleven members of the biotinylated sulfonate ester library possess the same X group (i.e., biotin), the same L group i.e., (i.e., N-(5-penylamine)-decanamido) and the same sulfonyl group (i.e., sulfonyl that has the structure -O-S(=O)$_2$-). Therefore, only the R group varies in this library. Furthermore, the R group only contains alkyl, aryl and heteroaryl groups.

With respect to adequate disclosure Applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples*, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Here, the Examiner contends that the successfully identification of one target protein (i.e., class I aldehyde dehydrogenase) via the use of one library of sulfonate esters is not "representative" of the full scope of Applicants claims. Applicants are only in possession of a method for the use of "activity based probes" wherein F = -SO3-; L = N-(5-penylamine)-decanamido; X is biotin and R represents small alkyl, aromatic and heteroaromatic groups. Furthermore, Applicants are not is possession of methods for identifying all target proteins (i.e.,

Applicants have only shown that they can identify a class I aldehyde dehydrogenase with this group of sulfonate esters).

The specification does not describe methods for making and/or using any specific "activity based probes" other than those mentioned above. Furthermore, Applicants successfully identified only one target protein (i.e., the class I aldehyde dehydrogenase mentioned above). The Examiner contends that there is no reason to "assume" that any other enzymes can be successfully identified in a similar fashion because Applicants have not provided any "general teachings" that would allow a person of skill in the art to extrapolate this method to other enzymes not yet tested i.e., Applicants have not shown that the method is "generalizable" (see below). Consequently, the Examiner contends that there is no teaching in the specification that would allow a person of skill in the art to determine *a priori* that applicants were in possession of the full scope of the claimed invention because Applicants have not provided any common distinguishing structural attributes that can link together ***all*** of the ***claimed*** probes and enzymes (that fall outside the narrow scope of Applicants examples).

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing a single example of a sulfonate ester library to identify a single example of a cALDH-I enzyme is insufficient to teach this broad genus. Furthermore, Applicants admit that a more "generalizable" correlation has not yet been achieved (see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes"

Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings"). This underscores an inherent problem with Applicants' claimed method in that Applicants have not provided any guidance for determining what "type" of compounds to screen and under what "conditions" they should be screened (i.e., Applicants have provided no starting point for the screening) to identify the majority of target proteins that fall within the scope of the current claims, nor have they provided any assurances that the claimed method will work for other systems. The fact that the sulfonate esters proved successful in screening cALDH-I does not mean that another "sulfonyl group" (e.g., sulfates, sulfinates, sulfamates, etc.) would do the same. Likewise, there is no guarantee that other "target proteins" (other than c-ALDH-I) will be identified using the presently claimed methods. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of examples to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

19. Claims 12, 14, 16-18 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for albumin-binding domain asparagine mutants, does not reasonably provide enablement for any asparagine "modified" proteinaceous ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The present claims are directed to the use of "non-directed" R*(F-L)-X activity based probes for screening combinatorial chemical libraries wherein X is "a ligand", "L- a bond or alkylene or an alkyleneoxy chain linking group", F is "a sulfonyl group" and R is "a group of less than 1 kDal." These claims represent broad scope because they would include an infinite number of methods for producing and/or using an infinite number of structural variants

(i.e., activity based probes) wherein no distinguishing structural attributes are provided for the "R" and "X" portions of the "activity based probes." The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "R" and "X" portions of the "activity based probes." Furthermore, Applicants' claims include method steps for the identification of an infinite number of "active target proteins" wherein no distinguishing structural features are provided for these proteins either. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Applicants admit that the art is inherently unpredictable (see Adam, G. C.; Cravatt, B. F.; Sorensen, E. J. "Profiling the specific reactivity of the proteome with non-directed activity-based probes" Chemistry & Biology 2001, 8, 81-95, especially conclusion on page 91, column 1, paragraph 1, "Finally, the discovery that sulfonate probes not only labeled cALDH-I in complex proteomes, but also inhibited this enzyme's catalytic activity suggests that, at least in this one example [i.e., Applicants make no promise that it will work for any other examples], a screen for heat-sensitive labeling events accurately identified a small molecule-protein reaction that impacted the protein's biological function. If this correlation proves generalizable [i.e., the correlation may NOT prove generalizable i.e., Applicants use the word "If"], non-directed approaches for profiling the specific reactivity of the proteome may [or may not] generate chemical reagents applicable for both proteomics investigations and cell-based functional screenings").

Therefore, the Examiner contends that the level of predictability in the art is low or absent.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants provide only one example of a "non-directed" library of "activity based probes" (i.e., containing eleven members of biotinylated sulfonate esters) that was useful in identifying one target protein (i.e., class I aldehyde dehydrogenase, cALDH-I, was irreversibly inhibited by the sulfonate library).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of

success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 12, 14, 16, 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Purohit et al (Purohit, A.; Williams, G. J.; Howarth, N. M.; Potter, B. V. L.; Reed, M. J. "Inactivation of Steroid Sulfatase by an Active Site-Directed Inhibitor, Estrone-3-O-Sulfamate" *Biochemistry* **1995**, *34*, 11508-11514).

For ***claims 12, 14, 16***, Purohit et al (see entire document) discloses a method for screening a library of estrones for potential inhibition of sulfatase enzymes (i.e., estrone sulfatase and dehydroepiandrosterone sulfatase) in placental microsomes and intact MCF-7 breast cancer cells (see Purohit et al, abstract; see also figure 1, compounds 4-6), which anticipates claims 12 and 14. Here, the combinatorial chemical library has the same formula as that disclosed by Applicants wherein the X group is "estrone", the L group is a "bond", the F group is "SO_2" or alternatively "SO_2N" and the R group varies in the library to include "NH_2, NHMe and NMe_2" or alternatively "H or Me" (see Purohit et

al, figure 1, compounds 4-6). Furthermore, Purohit et al discloses combining members of the library with a complex mixture (e.g., the placental microsomes and intact MCF-7 breast cancer cells that contain estrone sulfatase and dehydroepiandrosterone sulfatase) wherein conjugates are formed between the library members and the sulfatase proteins (see Purohit et al, page 11513, figure 8; see also Materials and Methods section). In addition, Purohit et al discloses isolating said conjugates from the active and inactive complex mixture (see Purohit et al, page 11509, column 2, paragraph 1). Finally, Purohit et al discloses comparing both "active" and "inactive" reaction mixtures (see Purohit et al, abstract, "The enzyme [sulfatase] is protected from inactivation by estrone sulfate [i.e., active form], which is also consistent with active site-directed inhibition. EMATE is proposed to inactivate estrone sulfatase by irreversible sulfamoylation of the enzyme [i.e., inactive form]"; see also page 11512, figure 6). Furthermore, Purohit et al discloses using two separate "portions" for the active and inactive mixture i.e., a "portion" with estrone sulfate added and a "portion" without any estrone sulfate added (see Purohit et al, page 11510, column 1, paragraph 1).

For ***claim 16***, Purohit et al discloses library members with different on-rates (see page 11510, Results, "Nature of EMATE Inhibition of Sulfatase Activity" section, especially column 2, paragraph 4).

For ***claim 20***, Purohit et al discloses R = alkyl (i.e., a methyl group) (see Purohit et al, page 11508, figure 1, compound 6).

For ***claim 21***, Purohit et al discloses F = sulfamate (see Purohit et al, page 11508, figure 1, compound 6).

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 12, 14, 16-18 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gygi et al (Gygi, S. P.; Rist, B.; Gerber, S. A. Turecek, F.; Gelb, M. H.; Aebersold, R. "Quantitative analysis of complex protein mixtures using isotope-coded affinity tags" *Nature Biotechnology* **1999,** 17, 10, 994-999) and Liu et al (Liu, Y.; Patricelli, M. P.; Cravatt, B. F. "Activity-based protein profiling: The serine hydrolases" *PNAS* **1999**, 96, 26, 14694-14699) and Bogyo et al (Bogyo, M.; McMaster, J. S.; Gaczynska, M.; Tortorella, D.; Goldberg, A. L.; Ploegh, H. "Covalent modification of the active site threonine of proteasomal β

subunits and the *Escherichia coli* homolog HSIV by a new class of inhibitors" *PNAS* **1996**, 94, 6629-6634).

For ***claims 12, 14, 16-18 and 20-24*** Gygi et al. disclosed a method for quantitative analysis of complex protein mixtures using isotope-coded affinity tags (ICAT) (Abstract; pg. 994, right col., 6-9). The method comprises of the following steps: (1) The side chains of cysteinyl residues in a reduced protein sample representing one cell state are derivatized with the isotopically light form of the ICAT reagent. The equivalent groups in a sample representing a second cell state are derivatized with the isotopically heavy reagent (refers to the combining step). (2) The two samples are combined and enzymatically cleaved to generate peptide fragments (refers to the sequestering step). (3) The tagged peptides are isolated by avidin affinity chromatography (refers to the determining step). (4) Finally, the isolated peptides are separated and analyzed by LC-MS/MS (electrospray ionization (ESI) MS/MS, in conjunction with microcapillary liquid chromatography (LC)) (pg. 994, right col., 12-24; figure 2) (refers to the comparing step).

The method of Gygi et al. does not expressly disclose that the probe can contain the structures disclosed by Applicants wherein F is a "sulfonyl group" and the target proteins are serine hydrolases.

The combined teachings of Liu et al and Bogyo disclosed a method of activity-based protein profiling using an active site directed probe (Abstract). The probe disclosed by Liu et al is a biotinylated fluorophosphonate, FP-biotin, (pg. 14694, left col., lines 30-33), but Bogyo et al discloses that the "sulfonyl groups" can also be used probes (see Liu et al, page 14699, column 1, paragraph 2, "Although we have demonstrated the utility of

a biotinylated fluorophosphonate as a rapid and high-sensitivity probe for detecting serine hydrolase activities directly from crude cell and tissue samples, one could envision that additional types of tagged irreversible inhibitors may succeed at labeling other classes of enzymes. For example, Bogyo and colleagues have recently used radiolabeled vinyl sulfones as selective reagents for marking members of the proteasome family of proteases (36) [wherein reference 36 refers to the Bogyo et al reference]"). The method steps of reacting protein samples (proteomic mixture) with FP-biotin (activity-based probe) include combining FP-biotin mixture with the protein samples and detecting the FP-biotin-reactive proteins by SDS/PAGE-Western Blotting (pg. 14695, right col., lines 26-64). The FP-biotin-reactive proteins are further analyzed by MALDI mass spectrometry (pg. 14696, left col., lines 11-15). FP-biotin can react with numerous serine hydrolyses (target enzyme) in crude cell and tissue samples (pg. 14698, left col., lines 1-8).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the biotinylated sulfones linked by N-(5-pentylamine)-decanamido probes as taught by the combined teachings of Liu et al and Bogyo et al in the method of Gygi et al because Bogyo et al, Gygi et al and Liu et al. disclose methods of detecting proteins from a crude cell samples (Gygi: pg. 994, right col., 6-9, and pg. 995, fig. 2; Liu: pg. 14698, left col., lines 1-8) (i.e., the references represent analogous art). One of ordinary skill in the art would have been motivated to include that the biotinylated sulfone probes and the target proteins disclosed by the combined teachings of Liu et al and Bogyo et al (e.g., serine hydrolases) in the method of Gygi et al. for the advantage of providing a probe that is specific for profiling in a single class of proteins

(Liu: pg. 14694, lines 30-33) since both Gygi et al. and Liu et al. disclose method of detecting proteins from a crude cell samples (Gygi: pg. 994, right col., 6-9, and pg. 995, fig. 2; Liu: pg. 14698, left col., lines 1-8). Furthermore, a person of skill in the art would have been motivated to combine the Bogyo et al and Liu et al references because Liu et al explicitly states that these two references should be combined (see Liu et al, page 14699, column 1, paragraph 2, "Although we have demonstrated the utility of a biotinylated fluorophosphonate as a rapid and high-sensitivity probe for detecting serine hydrolase activities directly from crude cell and tissue samples, one could envision that additional types of tagged irreversible inhibitors may succeed at labeling other classes of enzymes. For example, Bogyo and colleagues have recently used radiolabeled vinyl sulfones as selective reagents for marking members of the proteasome family of proteases (36) [wherein reference (36) refers to the Bogyo et al reference]").

Contact Information

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
September 1, 2003

BENNETT CELSA
PRIMARY EXAMINER